REMARKS

The claims have been amended to more clearly define that which applicants believe to be their invention. In particular the claims have been amended to clarify that the affinity of the claimed monoclonal antibody is based on its ability to bind to an amino acid epitope that lacks modification of the sequence YPYDVPDYA (including for example methylation of the amino acid sequence). Accordingly, applicants have amended the claims to specify that the monoclonal antibody binds with an affinity of >3 $X10^8M^{-1}$ to an epitope that is 13 or 14 amino acids in length wherein nine amino acids of the epitope consist of the sequence of SEQ ID NO: 1. Support for the amendment to claims 18 and 24 is found throughout the specification and more particularly at page 2, lines 24-25, page 3, lines 21-25, original claim 7 and Table 1 on page 9. Claims 18 and 19 have been further amended to remove the reference to the tradename BIOCORE®. New claims 26 and 27 have been added, and support for those claims is found on page 8, line 1 through page 9, line 5, particularly in Table 1.

Claims 18-21 stand rejected under 35 USC § 102(b) as being anticipated by, or in the alternative, rejected under 35 USC § 103(a) as obvious over Hinds et al. (Journal of Medicinal Chemistry, 1991 vol. 34 pages 1777-1789). Applicants respectfully traverse.

First of all, applicants note that the claims as amended now specify that the claimed isolated monoclonal antibody of the present invention has a binding affinity of greater than 3 X 10^8M^{-1} for an epitope that is 13 or 14 amino acids in length wherein a nine amino acid sequence of the epitope consists of the sequence of SEQ ID NO: 1. The two monoclonal antibodies (DB19/1 and DB19/25) isolated by Hinds et al. are reported as having dissociation constants of 1.8×10^{-7} and 1.8×10^{-8} (see Table IV on page 1784 of that reference) for the peptide sequence YPYDVPDYA (Pro-NAcP9). Accordingly, the Hinds antibodies have binding affinities (the

reciprocal of the dissociation constant) of only 5.5 x 10^6 and 5.5 x 10^7, respectively for the peptide sequence YPYDVPDYA (Pro-NAcP9).

The Examiner contends that Hinds discloses antibodies that have a dissociation constant ranging from 8.8 X 10^{-5} to 3.6 X 10^{-9} for peptides containing the sequence YPYDVPDYA. However, a careful review of Table IV reveals that the lowest dissociation constants listed for antibodies DB19/1 and DB19/25 (as referenced by the Examiner) relate to their binding to a modified (methylated) amino acid sequence, not to the peptide, Pro-NAcP9. As noted by Hinds, "On the other hand, the 2αMePro-NAcP9 **analogue** (2) bound with higher affinity to the two monoclonals than did NAcP9 (1)" (page 1784, second full paragraph, emphasis added). The lowest dissociation constant measured for the Hinds antibodies against NAcP9 (YPYDVPDYA) is 1.8 X 10^{-8}, which corresponds to a binding affinity of 5.5 X 10^7. Therefore, Hinds fails to teach an isolated monoclonal antibody that binds to the non-methylated amino acid sequence YPYDVPDYA (SEQ ID NO: 1) with a binding affinity greater than 3 X $10^8 M^{-1}$.

Applicants have amended their claims to clarify that the claimed antibodies bind with a high affinity to a 13 or 14 amino acid sequence that includes a nine amino acid sequence consisting of YPYDVPDYA, and not an amino acid analogue of YPYDVPDYA. More particularly, the claims have been amended to state that the antibody binds with an affinity greater than 3 X $10^8 M^{-1}$ to a 13 or 14 amino acid sequence wherein 9 amino acids of that sequence consists of the sequence YPYDVPDYA (SEQ ID NO: 1). Thus claim 18 as amended excludes the lower affinity antibodies of the Hinds, which bind to the non-methylated YPYDVPDYA sequence (NAcP9) at a binding affinity of 5.5 X 10^7 or less.

To anticipate, a reference must disclose each of the elements of the claimed invention. Applicants respectfully submit the Hinds reference fails to teach an isolated antibody that has the

required binding affinity. Accordingly, applicants request the withdrawal of the rejection based on 35 USC § 102(b).

Regarding the rejection of the claims for obviousness, the Examiner has stated that for a given antigen, the Kd "usually" varies from 10^{-7} M to 10^{-11}. In support of that statement the Examiner has made reference to a general survey immunology textbook.

First of all, applicants note that the antibodies disclosed by Hinds are monoclonal antibodies, thus there should not be a broad range of affinities for antibodies produced by a hybridoma cell line. Furthermore, applicants respectfully submit that experimenters typically select an antibody producing hybridoma from the available pool of hybridomas based on which hybridoma produces an antibody providing the strongest positive signal. Accordingly, one of ordinary skill would have reason to believe that two isolated antibodies DB19/1 and DB19/25 were the best antibodies produced by the Hinds et al methods. The possibility that the methods disclosed by Hinds could generate antibodies having the high affinities of applicants' claimed antibodies is mere speculation.

Furthermore, applicants respectfully submit that one of ordinary skill appreciates that such generic statements provided in survey textbooks (regarding the range of dissociation constants of antibody preparations) may be true when discussing the general characteristics of antibodies in the abstract. However, skilled practitioners know that the quality of antibodies generated for individual antigens is highly variable. Thus contrary to the Examiner's assertion, one of ordinary skill in the art would not anticipate that antibodies having an affinity ranging over four orders of magnitude (i.e. 10^{-7} M to 10^{-11}) will be generated for each antigen subjected to standard antibody production procedures.

Although the techniques underlying hybridoma technology are well recognized, the results obtained by the use of such techniques use are clearly unpredictable. Hybridoma technology is an empirical art in which the routineer is unable to foresee what particular antibodies will be produced and which specific surface antigens will be recognized by them. **Only by actually carrying out the requisite steps can the nature of the monoclonal antibodies be determined and ascertained; no "expected" results can thus be said to be present** (emphasis added). Ex parte Old, 229 USPQ 196 (BPAI 1985). Accordingly, as recognized by the USPTO Board of Patent Appeals and Interferences, the ability of producing the high affinity antibodies of the present invention could not have been expected, and therefore cannot be obvious, absent specific evidence showing they can be produced. However, the techniques for producing antibodies are sufficiently well characterized that results are reproducible once an antigen has been characterized.

The Examiner concludes that antibodies, having the high affinities of the present invention, can be produced using the methods disclosed in Hinds, without any supporting evidence or description in Hinds of an antigen that is capable of producing such a result. A reference to a generic discussion of antibody dissociation rates does not make applicants high affinity antibodies to the peptide YPYDVPDYA obvious, it merely constitutes an invitation to experiment. Hinds simply fails to teach the antigen and methods necessary to produce high affinity antibodies for the relevant target antigen. Applicants are the first to do so, as is described in Example 1 of the present invention.

Applicants have used a procedure and specific antigen that has resulted in the actual production of antibodies having a binding affinity of 10^{8}-$10^{10}M^{-1}$. Applicants respectfully submit that the Hinds et al reference fails to suggest that antibodies having a higher affinity than

those disclosed therein (i.e., greater than 5.5 X 10^7) could be obtained, and fails to provide a sufficient teaching of how to obtain such high affinity antibodies. Applicants respectfully submit that "obvious to try" is not the standard under 35 USC § 103, and that Hinds is merely an invitation to experiment. Accordingly applicants respectfully request the withdrawal of the rejection of the claims for obviousness.

Claims 18-21, 23 and 25 stand rejected under 35 USC § 112, first paragraph for failing to comply with the written description requirement. Applicants respectfully traverse.

First of all, applicants note that the claims are directed to an antibody that binds to its target antigen with a high affinity. The target antigen has been described with exact specificity in claims 26 and 27 and with a broader formula in claim 18. The Examiner references a passage from *The Guidelines for Examination of Patent applications Under 35 USC 112, paragraph 1. "Written Description" Requirement* that a genus embracing widely varient species cannot be achieved by disclosing only one species within the genus (page 9 of the office action). Clearly, applicants are not attempting to claim antibodies that embrace "widely varient species" but rather to a narrowly tailored target peptide (in the case of claim 18) or the actual amino acid sequence disclosed in claim 26.

The Examiner contends that "factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification" (page 8 of the Office Action). Clearly this statement is in error for applicants have described an actual reduction to practice in Example 1. Furthermore, applicants have deposited hybridoma cell line R 3A12 at the "Deutsche Sammlung fûr Mikroorganismen und Zellkulturen" under Accession No. DSM ACC2286 (08.10.1996), indicating a full description and possession of the claimed subject matter (see Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 965 (Fed. Cir. 2002). Thus the present specification

provides an actual reduction to practice, and the three specific clones characterized in Example 1 (R3F10, R3A12 and R6D12) establish that the methodology described in the present application can be used to generate multiple members of the claimed genus.

The Federal Circuit held in Noelle v. Lederman that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen" (see Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

Besides providing an actual reduction to practice by making a biological deposit, applicants have further described the claimed invention by reference to the antigen used to generate the antibodies. Contrary to the Examiner's assertions, applicants have provided a detailed description of the antigen used to generate the claimed antibodies, as detailed on page 6, lines 1-12. More particularly, the antigen used is a keyhole limpet hemocyanin (KHL)-coupled haemagglutinin protein (comprising either SEQ ID NO: 2 or SEQ ID NO: 3 as the HA protein). Applicants have even described the coupling reagent, maleinimidopropyl-N-hydroxysuccinimide ester (MPS), and the monomers added to the antigen during the course of peptide synthesis (CUZU and CUSU). One of ordinary skill would readily comprehend the complete structure of the disclosed antigen described in the present specification, as each of the abbreviated components of the antigen disclosed on page 6 is known. In particular, MPS, CUZU and CUSU are reagents known to those skilled in the art as indicated by their usage in US patent no. 6,613,530 (the specification which was published in February, 8, 1996) at column 15, lines 3-4 and in Example 1. In addition those skilled in the art are familiar with the use of KLH as a

hapten. Accordingly, applicants have provided a full description of the structure of the antigen used to prepare the claimed antibodies of the present invention.

As noted in Example 16 of *The Guidelines for Examination of Patent applications Under 35 USC 112, paragraph 1. "Written Description" Requirement* (66 FR 1099-1111, January 5, 2001):

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that **the spectrum of antibodies** which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X. (emphasis added).

Therefore in accordance with the US Patent Office's own Written Description Guidelines, applicants' description of their well characterized antigen entitles applicants to the full spectrum of antibodies that bind to that antigen. As demonstrated in Example 1 such antibodies have a binding affinity of greater than 3 $X10^{8}M^{-1}$. Accordingly the claimed invention is believe to fully comply with the written description requirement of 35 USC 112, first paragraph. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 18-21, 23 and 25 for failing to comply with the written description requirement.

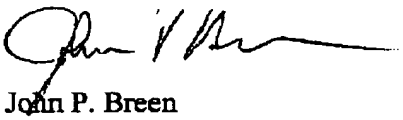
Claim 22 stands rejected under 35 USC § 112, second paragraph as being indefinite for the use of the phrase "A monoclonal antibody produced by hybridoma..." Applicants respectfully traverse and note that the hybridoma cell line presumably produces more than one antibody. The fact that the antibodies produced by the hybridoma are all of the same type and specificity does not negate the fact the hybridoma will produce many individual antibodies. However to advance the prosecution of the present application applications have amended claim

22 to replace "A" with "The". Accordingly, applications respectfully request the withdrawal of the rejection for indefiniteness.

Claims 18 and 19 have been amended to remove the reference to the tradename BIOCORE®, thus addressing the Examiner's objection to those claims as being indefinite.

Applicants believe that the present application is now in condition for allowance and such action is respectfully requested. If the Examiner has any questions or comments such that a conversation would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,



John P. Breen
Registration No. 38,833
Attorney for Applicants

(317) 261-7940
Indianapolis, Indiana 46204